PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
030811woMetg		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 03/04058	17.04.2003	18.04.2002

International Patent Classification (IPC) or both national classification and IPC

C12Q1/68

Applicant

EVOTEC NEUROSCIENCES GMBH ET AL.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the International application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.11.2003	09.07.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/04058

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally file and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34 as originally filed

Claims, Numbers

1-20 received on 06.05.2004 with letter of 06.05.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in th language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9,10,12, 16-19

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which doe not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclea that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opini could be formed.

   ☒ no international search report has been established for the said claims Nos. 9,10,12, 16-19

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide a or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicabilit citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-8, 11, 13-15 and 20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8, 11, 13-15 and 20
Industrial applicability (IA)	Yes:	Claims	1-8, 11, 13-15 and 20
	No:	Claims	

2. Citations and explanations

see separate sheet

V. Reasoned statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: WO 00 55318 A (UNIV BRITISH COLUMBIA ;XENON BIORESEARCH INC (CA)) 21 September 2000

D2: US-B1-6 225 525 (LEUNG WAI-PING ET AL) 1 May 2001

D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2001 (2001-07), VAISMAN BORIS L ET AL: 'ABCA1 overexpression leads to hyperalphalipoproteinemia and increased biliary cholesterol excretion in transgenic mice.' XP002237202 Database accession no. PREV200100378305 & JOURNAL OF CLINICAL INVESTIGATION, vol. 108, no. 2, July 2001 (2001-07), pages 303-309.

D4: US 2002 037843 A1 (LAM FRED CHIU-LAI ET AL) 28 March 2002

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 D1 discloses methods and products for the diagnosis of neurodegenerative diseases, including Alzheimer's disease (see pages 46 to 51). It is explained that ABCA1 may act as a transporter of APP products out of cells, and therefore be useful in the context of amyloidosis. It is explicitly disclosed that down-regulation of ABCA1 may lead to decreased apoptosis in neurodegenerative disorders (see page 46, lines 22-25).

2.2.2 In particular, D1 describes a method of diagnosing a neurodegenerative disease by determining the level and/or activity of an ABCA1 gene product. Antibodies against ABCA1 can be used in the development of diagnostic assays by monitoring the expression or biological activity of ABCA1 (see page 48, lines 18-27). Other tools can be used to monitor said expression, for example RT-PCR (see page 49, line 9). It is also described a method of evaluating a treatment by measuring the levels of expression of an ABCA1 gene product (see page 49, lines 15-24). Therefore, the methods of claims 1-7 and 20 are not new.

2.2.3 The fact that D1 deals as well with other types of ABCA-1 related diseases is not relevant for the question of novelty, since the passages cited above are explicitly directed to neurodegenerative diseases, including Alzheimer's disease (see for

example page 46, line 6; or claim 34). Nevertheless, it must be noted that the reference to neurodegenerative diseases in the present claims is not restricted to Alzheimer's disease.

2.2.4 The kit of present claim 8 is not new because its single component, a reagent "that selectively detects a transcription product of the ABCA1 gene", was known at the time of filing. Any polynucleotide comprising any fragment of the ABCA1 gene falls under the scope of such definition, and examples can be found in D2 and D3, among others. The features characterizing the method in which the kit is to be used ("by detecting [...] health status") represent merely an indication of intended use in the context of a product claim. This IPEA considers the use of the product as an optional feature not limiting the scope of a product claim. Therefore, claim 8 is not new.

2.2.5 D2 discloses a recombinant non-human animal comprising a non-native gene sequence coding for ABCA1 which is *obtainable by* the process described in claim 11 (see Abstract and Figure 1). Therefore, claim 11 is not new. The fact that the recombinant animal is used as a model for other purposes is irrelevant to the question of novelty of a product claim (see above).

2.2.6 D1 discloses drug screens for modulators of neurodegenerative diseases, including Alzheimer's disease. The methods are based on the modulation of expression levels of ABCA1 gene products (see page 47, line 5, to page 48, line 17; claim 34), not only in cells (see page 54), but also in test animals (see page 59). Therefore, the methods of claims 13-15 are not new.

2.2.7 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-8, 11, 13-15 and 20 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.3 SUFFICIENCY OF DISCLOSURE, CLARITY AND SUPPORT (Arts. 5 and 6 PCT)

2.3.1 Article 6 PCT requires that the matter for which protection is sought be defined in the claims in a clear and concise manner, and that all the claims be supported by the description. The support by the description must be sufficiently clear for the skilled person to put the invention as claimed into practice without undue burden, i.e. no more than a reasonable amount of experimentation, and without applying inventive skill.

2.3.2 The current application documents demonstrate that ABCA1 mRNA is underexpressed in the post-mortem frontal cortex of Alzheimer patients, when compared to its expression in the post-mortem temporal cortex of the same patients. However, the scope of the subject-matter claimed covers the prognosis, diagnosis, monitoring and evaluation of any neurodegenerative disease by measuring the levels or activities of any genetic product of the ABCA1 gene. The discrepance between the claimed scope of protection and the actual teaching of the description is evidenced by the following:

2.3.2.1 The fact that any translation product of the ABCA1 gene provides a reliable and reproducible marker for Alzheimer disease is not credible because the regulation of transcription does not necessarily produce an analogous regulation of the protein levels or activities; protein activity can be regulated at multiple further levels: splicing, translation, intracellular localization, modulation by ligands, degradation/turnover, etc. the application does not provide any scientific evidence that the protein levels of ABCA1 are also reduced in the frontal cortex of patients, let alone the expression of "fragments" and "variants", or their activities.

2.3.2.2 The very different nature and etiology of the wide range of diseases under the label of "neurodegenerative" makes extremely unlikely, in the absence of experimental support, that a down-regulation of the ABCA1 mRNA can be considered a reliable and reproducible marker for all of them.

2.3.2.3 The fact that ABCA1 mRNA is down-regulated in post-mortem tissue of Alzheimer patients when comparing frontal vs. temporal cortex does not necessarily mean that said levels will be regulated in the same manner in the

body fluids of an Alzheimer patient when compared to a healthy person. First, the application does not provide any evidence that ABCA1 mRNA can be detected in body fluids or tissue samples which are suitable for prognosis, diagnosis, monitoring, etc. And second, if said mRNA could be detected, there is no evidence that it would be down-regulated when compared to the levels of a healthy person.

2.3.2.4 The fact that post-mortem tissue samples of Alzheimer patients show this differential mRNA expression does not imply that a person at risk of developing Alzheimer, but without any symptoms, will show the same effect, even if molecular analysis of his brain tissue was possible. There is no scientific evidence in the application in support of the prognostic methods.

2.3.3 Considering these facts, this IPEA has reasonable doubts concerning first, the reproducibility of the invention as claimed, and second, the burden of experimentation and inventive skill necessary to carry out the invention over the whole claimed area. Therefore, the present application cannot be considered sufficiently disclosed in the sense of Article 5 PCT. For the same reasons, and despite being formally supported by the description, the present claims cannot be considered supported in the sense of Article 6 EPC.